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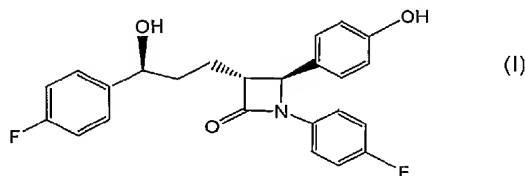
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(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF EZETIMIBE



(57) Abstract: The present invention relates to a cost effective and industrially advantageous process for the preparation of (3R,4S)-1-(4-fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, referred to here as Ezetimibe, it is represented as formula (1).

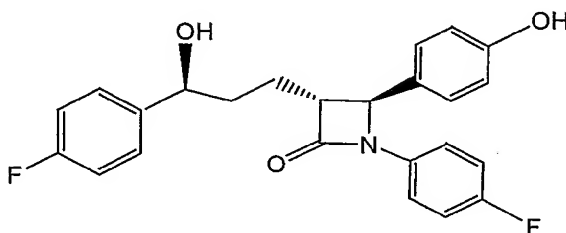


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IMPROVED PROCESS FOR THE PREPARATION OF EZETIMIBE

Field of the invention

The present invention relates to cost effective and industrially advantageous process for the preparation of (3R,4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, referred to here as Ezetimibe. It is represented as Formula-1.



Formula-1

Background of the invention

This invention relates to an improved, cost effective and industrially advantageous process for the preparation of (3R, 4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone (Ezetimibe), useful as cholesterol absorption inhibitor, claimed in U.S.Pat. No. 5,767,115. Preparation of Ezetimibe is also described in the above said patent. It comprises of (S)-4-phenyl-2-oxazolidinone is reacted with methyl-4-(chloroformyl)butyrate to obtain a compound of ester and it is condensed with 4-benzyloxy benzylidene (4-fluoro) aniline in the presence of titanium isopropoxide and titanium tetrachloride to give an amide compound and it is cyclised in the presence of tetrabutyl ammonium fluoride and bis trimethyl silyl acetamide to give protected lactam, it undergoes hydrolysis to give a carboxylic acid and further it reacts with p-fluoro phenyl magnesium bromide and zinc chloride in the

presence of tetrakis (triphenyl phosphine) palladium to give an aromatic ketone, it is further reduced selectively in the presence of chiral catalyst to obtain an hydroxy compound and it undergoes debenzylation to give the title compound of formula-I.

By following the above process in the hydrolysis stage after completion of the reaction, pH adjusted to acidic side (below pH- 4) and extracting the compound resulted more impure product because as the Lactam ring is acid sensitive, it is opened up while adjusting the pH to below 4. In the organometallic condensation reaction between acid chloride and para fluoro phenyl zinc halide, tetrakis (triphenyl phosphine) palladium is used as a catalyst which is highly expensive as well as molecular weight is higher which resulted in more byproducts and obtained compound is less pure.

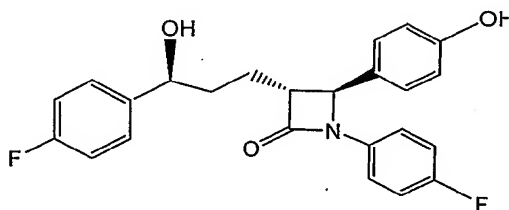
The above said process is both uneconomical, inconsistency in reproducibility and more of byproduct/waste generation like triphenyl phosphine oxide, DMS, etc., and hence it is not suitable for commercial production.

Therefore, the main objective of the present invention is to prepare formula-1 through a process which is cost-effective, commercially viable, eco-friendly and consistent.

The formula-1 is prepared in the present invention, in a novel process that is cost effective and suitable for commercial scale up.

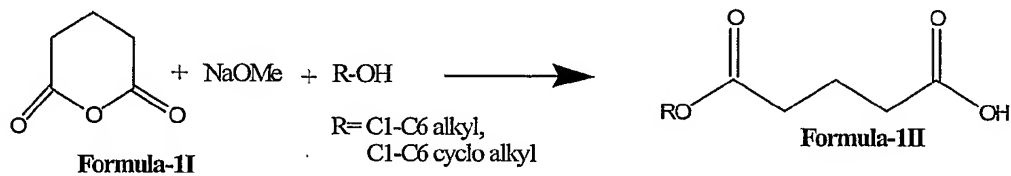
Summary of the invention

This invention provides an improved simple and cost effective, eco-friendly and well suited for commercial scale up of (3R,4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3 -hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, referred to here as Ezetimibe. It is represented as Formula-1.

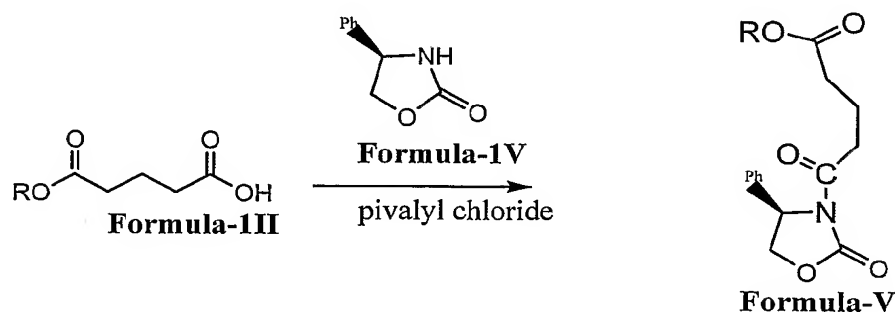
**Formula-1**

Comprising:

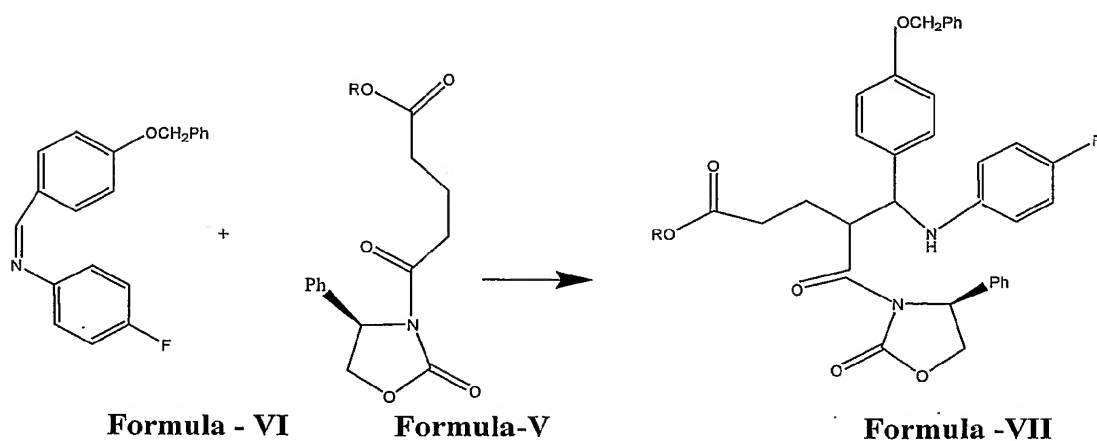
- (a) Glutaric anhydride of formula-II reacting with an aliphatic or alicyclic alcohol in Presence of a base to give ester compound of formula-III.



- (b). Using pivalyl chloride in the preparation of compound having the structural formula-V, by reacting it with compound of formula-III in presence of a acid trapping agent and subsequent reaction with chiral auxiliary of formula-IV

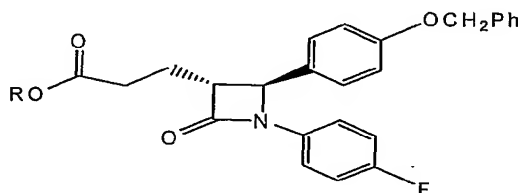


- (c) Reacting the ketone of Formula-V with benzylated imine of formula-VI in presence of Lewis acid to obtain an amide of formula-VII.



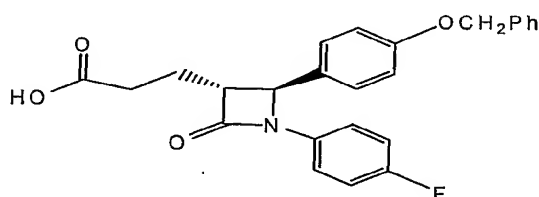
(d) Cyclizing the amide of formula VII with

- (i) a silylation agent and a fluoride ion catalyst as a cyclizing agent.
- (ii) A strong non-nucleophilic base to obtain the compound of formula-VIII.



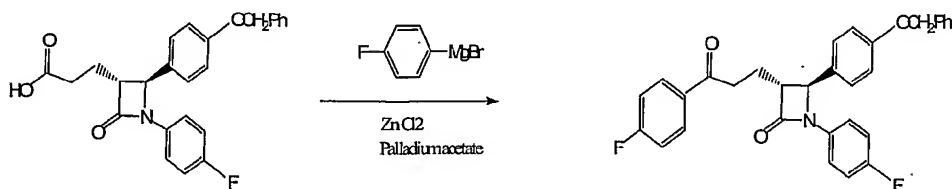
Formula-VIII

- (e). Hydrolising the ester group in formula VIII with a base in a suitable solvent to give the carboxylic acid compound of formula-IX. Adjusting the pH to 5 - 7 of hydrolysis reaction mass, preferably 6.5 to 7.0 and extraction of carboxylic acid compound of formula-IX.



Formula-IX

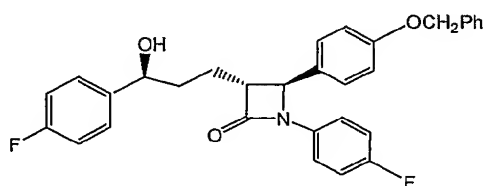
- (f). Compound of formula-IX is converted into acid chloride and further it is converted into formula-X by organo metallic reaction in presence of a Palladium acetate as catalyst.



Formula- IX

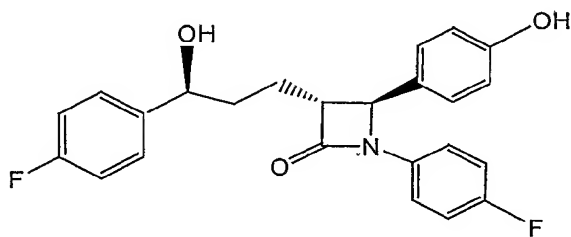
Formula- X

- (g). Reducing the aromatic ketone of formula-X in the presence of a chiral reducing agent or reducing agent in presence of a chiral catalyst to obtain hydroxy compound of formula-XI.



Formula-XI

- (h). Debenzylation of the compound of formula-XI with Pd/C to give the compound of formula-I.

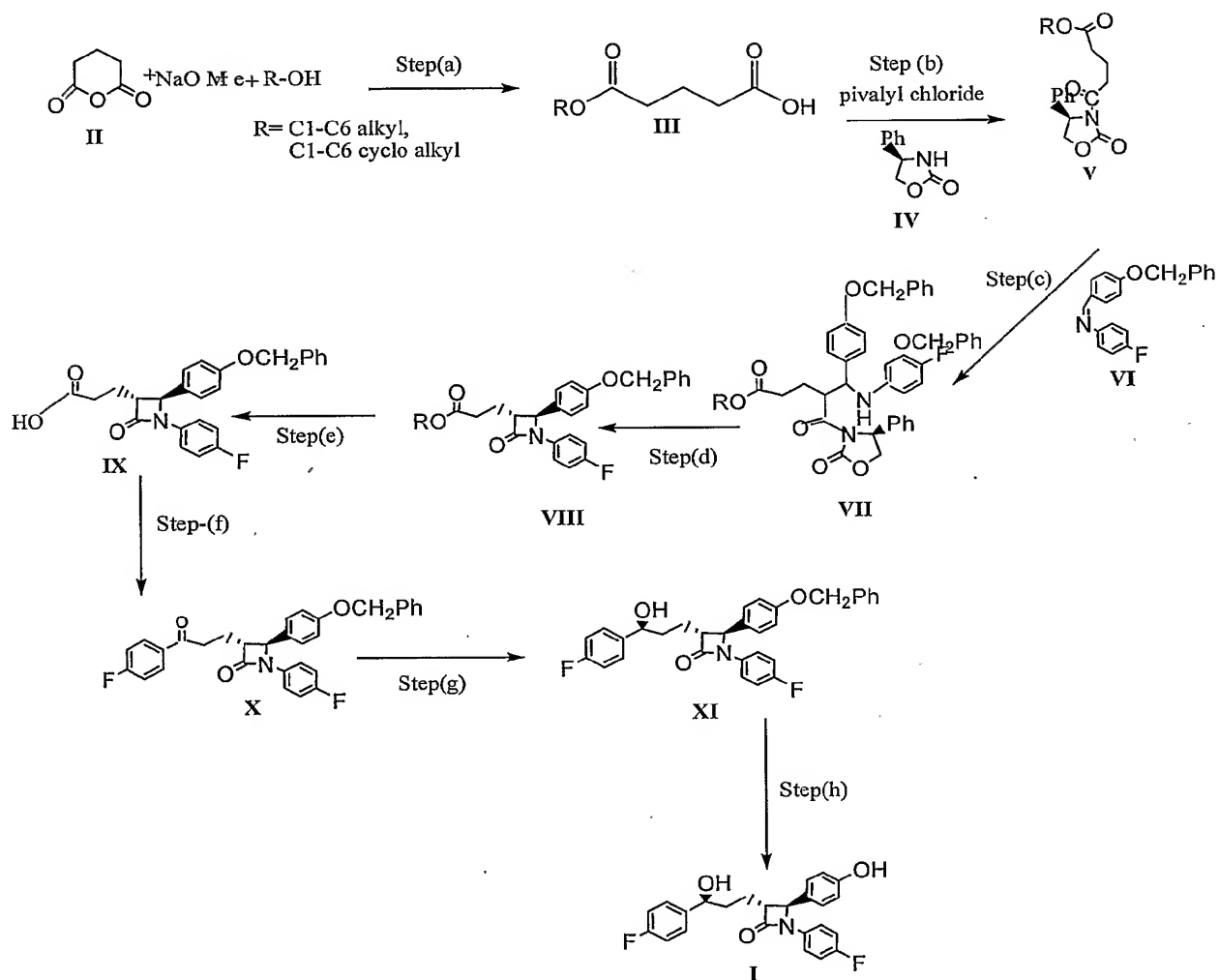


Formula-I

Detailed description of the invention

The present invention relates an improved process for the preparation of (3R,4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, referred to here as (Ezetimibe).

The process of the present invention is schematically represented as follows.



Comprising:

- a. Reacting Glutaric anhydride of structural formula-II with an aliphatic alcohol or alicyclic alcohol in presence of a base sodium methoxide to give compound of formula-III.
- b. Reacting the formula-III with pivalyl chloride in presence of an acid trapping agent like triethyl amine, diisopropyl ethyl amine or inorganic bases like sodium carbonate, potassium carbonate and further it is reacting with a chiral auxiliary of formula-IV to give ketone compound of structural formula of V.
- c. Ketone compound of formula-V is further condensed with an benzylated imine of formula-VI to give the an amide compound of formula-VII in presence of a Lewis acid.
- d. Cyclising the amide of formula-VII with a silylating agent and a fluoride ion catalyst as a cyclising agent to give the protected lactam compound of formula-VIII.
- e. Hydrolysis of protected lactam compound of formula-VIII with a base to give the carboxylic acid of formula-IX.
- f. Carboxylic acid of formula-IX is converted into acid chloride with oxalyl chloride and it is further condensed with para bromo fluoro benzene through organo metallic reaction to give the aromatic ketone of formula-X.
- g. Reducing the ketone of formula-X with chiral reducing agent or in the presence of a chiral catalyst to give chiral alcohol of formula-XI.
- h. Debenzylation of formula-XI with Pd/C to give the compound of formula-I.

Step-a: The reaction is carried out at a temperature -20°C to 65°C , preferably at $25-35^{\circ}\text{C}$ for 30 minutes to 15 hrs, preferably 6-8 hrs.

Step-b: pivalyl chloride reaction is carried out in a suitable solvent like dichloromethane, toluene, xylene, preferably in dichloromethane, in presence of an acid trapping agent such as triethyl amine, diisopropyl amine or inorganic base like NaHCO_3 , Na_2CO_3 , K_2CO_3 , preferably triethyl amine. Reaction is conducted at a temperature of -10°C to 50°C preferably at $15-30^{\circ}\text{C}$ for 1 to 10 hrs, preferably for 2-4 hrs.

Chiral auxiliary such as the compound of formula-IV is used like S-POZ, S-BOZ, preferably S-POZ. This reaction is carried out in presence of dimethyl amino pyridine as a catalyst at the temperature of $10-50^{\circ}\text{C}$, preferably at $40-50^{\circ}\text{C}$ for 30 minutes to 10 hrs, preferably 4-6 hrs.

Step-c: Condensation reaction of step-c can be carried out in a suitable solvent like dichloromethane, toluene, xylene, preferably dichloromethane and treated with a Lewis acid such as TiCl_4 at about -60 to 0°C , preferably at about -25°C , under a dry, inert atmosphere like nitrogen or argon. A tert. amine base such as diisopropyl ethyl amine is used as a trapping agent. This reaction is conducted for 3-6 hrs at -25 to -10°C , preferably about 4 hrs or until reaction is completely by TLC.

Step-d: The cyclisation of step-d can be carried out in a suitable solvent like dichloromethane, toluene, xylene, ethyl acetate, preferably in toluene at a temperature 0°C to 80°C , preferably at $40-50^{\circ}\text{C}$ with silylating agent like bis trimethyl silyl acetamide and a cyclising agent like tetra butyl ammonium fluoride.

Step-e: Hydrolysis of formula VIII with a suitable solvent like an alcohol solvent like ethanol, isopropyl alcohol, tert-butanol or ketonic solvents like acetone, methyl isobutyl ketone, preferably in acetone with a base like alkali and alkaline earth metal hydroxides, preferably sodium hydroxide at a temperature 0°C to 50°C , preferably at $25-35^{\circ}\text{C}$ for 30 minutes to 10 hrs, preferably 2-3 hrs to obtain a carboxylic acid of formula IX. Adjusting the pH to 5 - 7 of reaction mass, preferably 6.5 to 7.0 and extraction of carboxylic acid compound.

Step-f: Converting the Carboxylic acid of formula-IX into acid chloride using acid halogenating agent like, oxalyl chloride, thionyl chloride and phosphorous halides, preferably with oxalyl chloride and with a suitable solvent like dichloromethane, toluene, xylene or ethyl acetate, preferably dichloromethane. This reaction is carried out in an inert atmosphere like nitrogen at 0-40°C for 10 minutes to 5 hrs. Preferably at 25-35°C for 1-3 hrs

Acid chloride is further condensed with a Grignard reagent (it is prepared from the reaction of para bromo fluoro benzene with magnesium turnings to form 4-fluorophenyl magnesium bromide and it is further converted to 4-fluorophenyl zinc halide with anhydrous zinc chloride) in presence of a transition metal catalyst namely palladium acetate to give the condensed product as formula X. This reaction is carried out with a suitable solvent like dichloromethane, toluene, xylene or ethyl acetate, preferably toluene. This reaction is carried out in an inert atmosphere like nitrogen at -10 to 40°C for 10 minutes to 3.00 hrs. Preferably at 10-15°C for 30-60 minutes.

Step-g: Reduction of ketone of formula-X to hydroxy group using a chiral reducing agent such as DIP Chloride or reducing agent Borane THF or Borane-DMS, in the presence of a chiral catalyst such as (R)-tetrahydro-1-methyl-3,3-diphenyl-1H-pyrrol (1,2-c)(1,3,2) oxaza – borolidine (R-Methyl CBS) or R-Butyl CBS or R-Phenyl CBS. This reaction is carried out with a suitable solvent like dichloromethane, toluene, xylene or ethyl acetate, preferably toluene. This reaction is carried out in an inert atmosphere like nitrogen at -10 to 40°C for 30 minutes to 10 hrs. Preferably at 0 to 5°C for 2-3 hrs.

Step-h: Debenzylation of formula-XI with palladium carbon to give the title compound of formula-I. This reaction is carried out with a suitable solvent like an alcoholic solvents like methanol, IPA, tert-butanol or dichloromethane, toluene preferably in IPA. This reaction is carried out at 10 to 70°C for 30 minutes to 10 hrs. Preferably at 45 to 50°C for 2-3 hrs.

The examples mentioned below demonstrate specific preparations of the present invention. The examples are provided to illustrate the details of the invention and should not be constrained to limit the scope of the present invention.

EXAMPLE:1

Preparation of (3R,4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, referred to here as Formula-1.

Step-a: Preparation of Monomethyl glutarate (formula-III)

Taken 100 gm of glutaric anhydride of formula-II and methanol (250 ml) and sodium methoxide (1 gm) in a 1 lit round bottom flask and stirred for 6 hrs at 25-35°C. Distilled the solvent completely under vacuum at below 60°C. Residue is taken to next stage directly without any purification. Yield: 125 gm

Step-b: Preparation of ketone compound of formula-V

Formula -III material (45 gm) is dissolved in dichloromethane (225 ml) in 1 lit cleaned RBF. Added triethyl amine to the reaction mixture and stirred for 10 minutes. Pivaloyl chloride is added to the reaction mass in 45 minutes at 25-35°C. Maintained the reaction mass for 2 hrs. Added S-POZ (formula-IV), DMAP and DMF to the refluxed the reaction mixture for 7 hrs. Reaction mixture is quenched with water and separated the organic layer. Organic layer washed with water (100 ml) and distilled the solvent completely under vacuum and recrystallised the material in pet-ether. Yield: 50 gm.

Step-c: Preparation of compound of formula-VII.

Titanium tetrachloride (18 ml) and dichloromethane (600ml) were taken into a clean RBF, cooled the reaction mixture to 0°C and added titanium isopropoxide (16 ml) at 0-5°C. Dissolved the Formula-V material (50 gm) in dichloromethane and added to the reaction mass at 0-5°C and maintained the reaction mass for 15 minutes. Diisopropyl ethyl amine (65 ml) is added to the reaction mixture and maintained for 45 minutes and cooled to -20 to -10°C and charged the benzylated imine (92 gm) of formula-VI to the reaction mixture, maintained for 4 hrs at -20 to -10°C. Quenched the reaction with acetic acid and washed the organic layer with sulfuric acid solution, distilled the solvent completely and material is recrystallised in methanol. Yield: 65 gm.

Step-d: Preparation of compound of formula-VIII (Cyclisation)

Taken toluene (100 ml) and compound of formula VII (25 gm) into cleaned RB.Flask, heated to 45°C and added N,O-bis trimethyl silyl acetamide(17 gm) and TBAF.3 H₂O (1.1 gm) and maintained for 2 hrs at 45-50°C. Reaction mass is quenched with methanol and washed with 1 N Hcl solution, 1N sodium bicarbonate solution followed by saturated sodium chloride solution, distilled the solvent completely under vacuum and toluene is charged and isolated Rec S-POZ, filtrate is concentrated and product is isolated in methanol and dried the product at 50-60°C. (Yield: 13 gm). M.R 60-65°C.

Step-e: Preparation of compound of formula-IX.

Compound of formula-VIII (25 gm) is dissolved in acetone (25ml) in a cleaned R.B.Flask. Water (62.5 ml) and sodium hydroxide (2.8 gm) added to the reaction mass. Maintained the reaction mass for 3 hrs at ambient temperature. Reaction mass quenched with water and pH adjusted to 6.5-7.0 with aqueous hydrochloric acid. Reaction mass extracted with ethyl acetate and distilled the solvent completely under vacuum to give residue of the compound. It is used into next stage without any purification. Yield: 22 gm.

Step-f: Preparation of compound of formula-X.

Compound of formula-IX (25gm) is dissolved in dichloromethane in a R.B.Flask. and catalytical amount of Dimethyl formamide is added. Oxalyl chloride is slowly added at ambient temperature, maintained the reaction mass for 3 hrs at ambient temperature. Distilled the solvent completely under vacuum and toluene is added and again distilled completely under vacuum. Toluene is added to the crude and cooled to 10-15°C and then the palladium acetate and maintained for 15 minutes.

4-fluorophenyl magnesium bromide is taken in another vessel under nitrogen atmosphere and cooled to 0 -5°C and added anhydrous zinc chloride and stirred for 1 hr. This complex is added to the acid chloride reaction mass at ambient temperature and maintained for 45 minutes. Filtered the reaction mass through hyflow and washed with toluene and THF mixed solution. Distilled the solvent completely under vacuum, added dichloromethane and silica gel to the crude and distilled the solvent completely under vacuum. Cyclohexane is added to the silicagel mixture and stirred for 30 minutes and filtered and washed with cyclohexane. Silicagel mixture is slurried with ethyl acetate and cyclohexane. Distilled both filtrates under vacuum to get the residue. (Yield:18 gm).

Step-g:**Example-1: Preparation of compound of hydroxy compound of formula-XI.**

Taken toluene (250 ml) into cleaned R.B.Flask under nitrogen atmosphere and cooled to 0-5°C. Borane DMS complex and (R)-tetrahydro-1-phenyl-3,3-diphenyl-1 H,3H-pyrrol (1,2-c)(1,3,2) oxaza borolidine (R-phenyl CBS) is charged into the reaction mass at 0°C. 25 gm of Keto compound of formula-X is dissolved in toluene(50 ml) and added to the reaction mass at 0-5°C. Maintained the reaction mass for 3 hrs and quenched with methanol and followed by 1 N hydrochloric acid solution. Organic layer separated and washed with 5% hydrogen peroxide solution and 5% sodium sulfate solution and followed by with 10% sodium chloride solution. Distilled the solvent completely under reduced pressure at below 75°C. Product is isolated in diisopropyl ether and dried the product at 60-70°C for 6 hrs. (Yield:15 gm).

Example-2: Preparation of compound of hydroxy compound of formula-XI.

Taken toluene (250 ml) into cleaned R.B.Flask under nitrogen atmosphere and cooled to 0-5°C. DIP Chloride (Mole ratio 1:1.5) into the reaction mass at 0°C. 25 gm of keto compound of formula-X is dissolved in toluene(50 ml) and added to the reaction mass at 0-5°C. Maintained the reaction mass for 3 hrs and quenched with ammonia solution. Organic layer separated and washed with 10% sodium chloride solution. Distilled the solvent completely under reduced pressure at below 75°C. Residue is taken for next stage directly without any purification.

Step-h: Preparation of compound of formula-I (Ezetimibe).

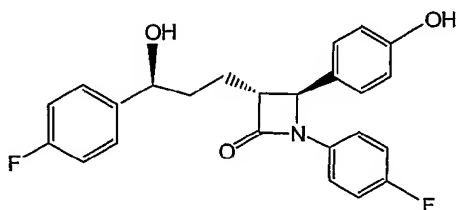
Taken compound of formula-XII (10 gm) and isopropanol (100 ml) into a hydrogenation flask, added 5 % Pd/C (4gm) at 25°C and maintained at 45-50°C for 3 hrs under hydrogen pressure, filtered through hyflow and washed the Pd/C with isopropanol(20 ml). Distilled the solvent completely under vacuum at below 70°C, product is recrystallised in dichloromethane (Yield: 6 gm).

Purification of Ezetimibe (formula-1).

Ezetimibe (10 gm) is dissolved in 30 ml of methanol and filtered through hyflow and saturated with DM. Water(30 ml) and stirred for 1 hr at 20-25°C. Product filtered and dried for 6-8 hrs at 80-85°C (Yield:9 gm).

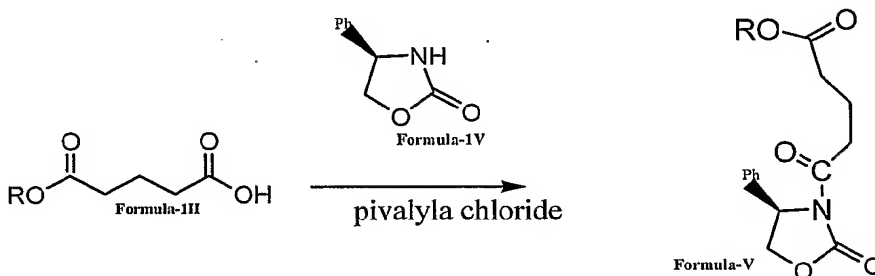
WE CLAIM:

1. A process for the preparation of (3R,4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3 -hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone of structural Formula-1 (Ezetimibe).

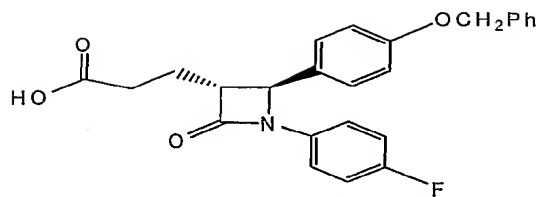


which comprises of:

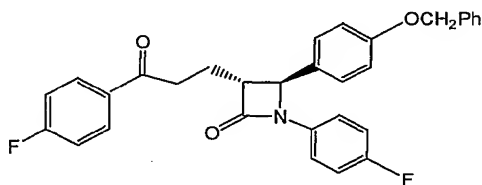
- i. Using pivalyl chloride in the preparation of compound having the structural formula-V, by reacting it with compound of formula-III in presence of a acid trapping agent and subsequent reaction with chiral auxiliary of formula-IV



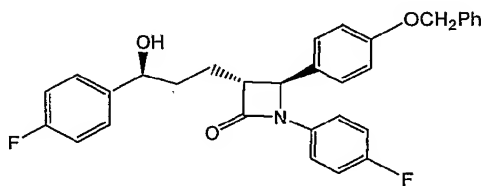
- ii. Hydrolysing the ester group in formula VIII (step-e) with a base in a suitable solvent to give the carboxylic acid compound of formula-IX
- iii. Adjusting the pH to 5 - 7 of hydrolysis reaction mass (Step-e), preferably 6.5 to 7.0 and extraction of carboxylic acid compound of formula-IX.

**Formula-IX**

- iv. Carboxylic acid compound of formula-IX on reaction with oxalyl chloride (step-f) and subsequent reaction with para fluoro phenyl zinc halide in presence of a transition metal acetates or halides to give the aromatic ketone of formula-X.

**Formula-X.**

- v. Reducing the aromatic ketone of formula-X in the presence of a chiral reducing agent or reducing agent in presence of a chiral catalyst to obtain hydroxy compound of formula-XI (step-g).

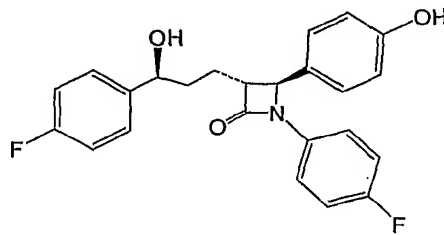
**Formula-XI**

2. The process according to claim-1, wherein step (b) reaction is carried out in a suitable solvent from the group consisting of dichloromethane, chloroform, toluene, ethyl acetate and mixture (s) thereof, preferably dichloromethane.
3. The process according to claim-1, wherein step (b), acid trapping agent is like triethyl amine, diisopropyl ethyl amine or inorganic bases like sodium carbonate, potassium carbonate, preferably acid trapping agent is triethyl amine.
4. The process according to claim-1, wherein step (b) reaction with a chiral auxiliary, where in chiral auxiliary is S-POZ or S-BOZ., preferably S-POZ.
5. The process according to claim 1, wherein step- (e), solvent is selected from the group consisting of alcohol's like ethanol, IPA, tert-butanol or ketonic solvents like acetone, methyl isobutyl ketone and mixture (s) thereof, preferably acetone.
6. The process according to claim 1, wherein step (e) the base is alkali or alkaline earth metal alkoxides or alkali or alkaline earth metal hydroxides, carbonates or bicarbonates, preferably alkali metal hydroxide, most preferably sodium hydroxide.
7. The process according to claim-1, wherein step (f) is carryout in presence of a transition metal catalysts like palladium, cobalt, nickel, iron, rhodium having its anionic part either halides or acetates.
8. The process according to claim-8, wherein the palladium catalyst is palladium acetate or palladium chloride, preferably palladium acetate.
9. The process according to claim-1, wherein step (g) is carryout in a suitable solvent at ambient temperature, wherein the solvent is selected from the group consisting of dichloromethane, toluene, xylene or ethyl acetate and mixture (s) thereof, Preferably solvent is toluene.
10. The process according to claim 1, wherein (step-g) the chiral reducing agent is DIP Chloride.
11. The process according to claim 1, wherein (step-g) the chiral catalyst is R-Butyl CBS or R-phenyl CBS.
12. A process for the preparation of (3R,4S)-1-(4-Fluorophenyl)-3-[3(S)-3-(4-fluorophenyl)-3 -hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, as here in described and exemplified.

AMENDED CLAIMS

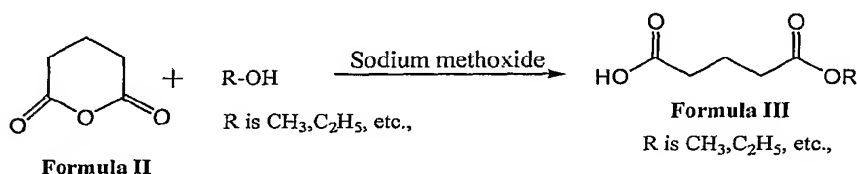
received by the International Bureau on 15 August 2006 (15.08.06)

1. An improved process for the preparation of (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone (Ezetimibe) compound of formula (I).

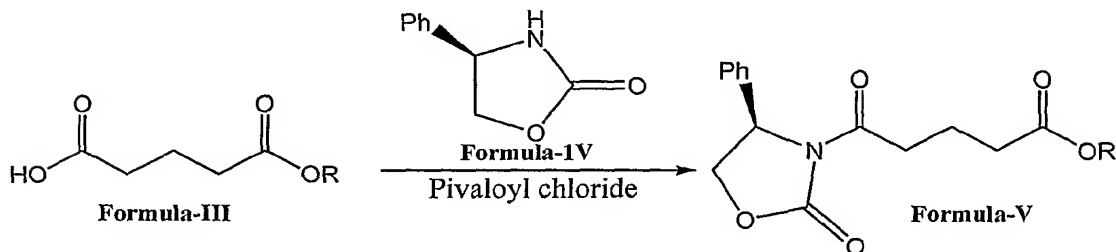
**Formula-1**

Which comprises of

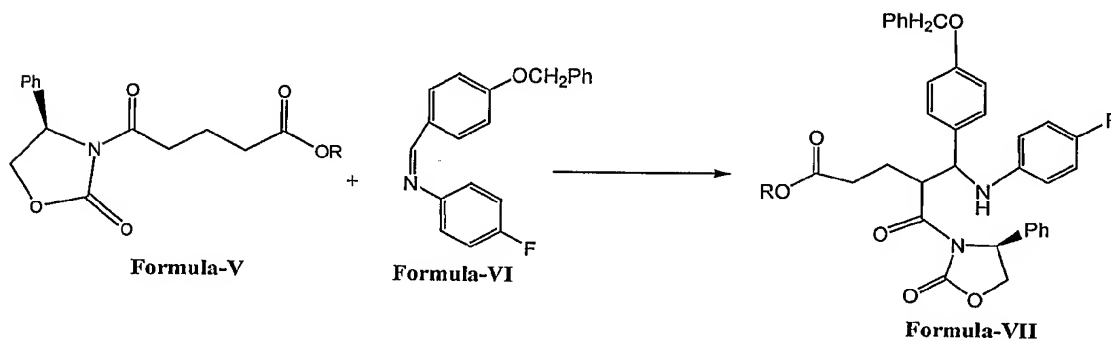
- a) Reacting glutaric anhydride compound of formula-II with linear or branched chain aliphatic C1-C6 alcohols like methanol, ethanol, propanol, isopropanol etc., preferably methanol in presence of a base like sodium methoxide, sodium hydroxide, potassium hydroxide, preferably sodium methoxide to give alkyl ester compound of formula-III,



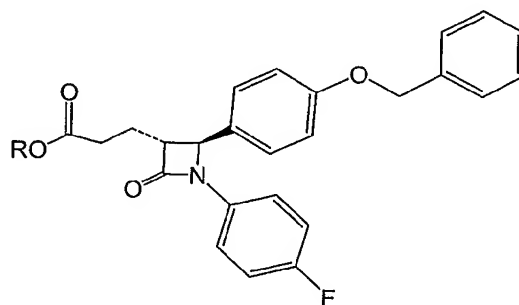
- b) Reacting the compound of formula-III with pivaloyl chloride in presence of an acid trapping agent like triethyl amine, diisopropyl ethyl amine, preferably tri ethyl amine and subsequent reaction with chiral auxiliary compound of formula-IV to give ester compound of formula-V,



- c) Reacting the ester compound of Formula-V with benzylated imine compound of formula-VI in presence of Lewis acid such as titanium tetrachloride, zinc chloride etc., preferably titanium tetrachloride in combination with titanium isopropoxide to obtain an amide compound of formula-VII,



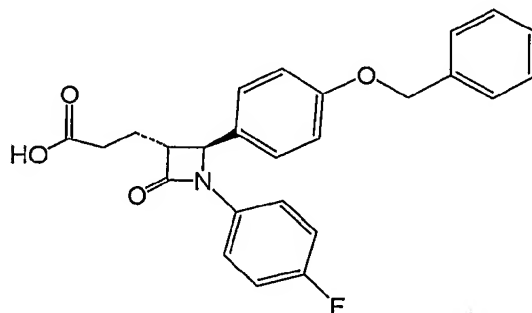
- d) Cyclizing the amide compound of formula-VII with a silylating agent like N,O-bis trimethyl silyl acetamide, N,O-bis (trimethylsilyl) trifluoro acetamide, preferably N,O-bis trimethyl silyl acetamide and a fluoride ion catalyst cyclizing agent like tetra butyl ammonium fluoride in a suitable solvent like methylene chloride, toluene, xylene, ethylacetate, preferably in toluene to obtain the compound of formula-VIII.



Formula-VIII

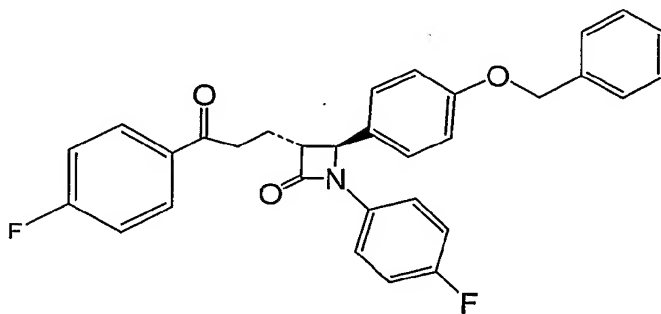
- e) Hydrolysing the ester group of compound of formula VIII with a base such as alkali or alkaline earth metal hydroxides like sodium hydroxide, potassium hydroxide, preferably sodium hydroxide in a suitable solvent such as alcohol solvents like ethanol, isopropyl alcohol, tertiary butanol or ketonic solvents like

acetone, methyl isobutyl ketone, preferably ketone solvents, more preferably acetone followed by adjusting the pH of the reaction mixture to 5 - 7, preferably 6.5 to 7.0 and extracting the carboxylic acid compound of formula-IX,



Formula-IX

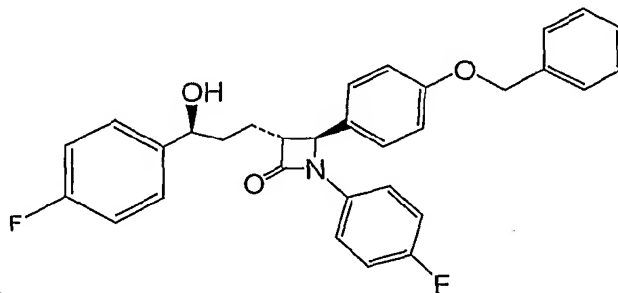
- f) Reacting the compound of formula-IX with an oxalyl chloride in a suitable solvent like methylene chloride, toluene, xylene, ethyl acetate, preferably methylene chloride affords acid chloride compound which in situ reacting with 4-fluorophenyl zinc halide in presence of a transition metal acetate or halide in a suitable solvent like methylene chloride, toluene, xylene, ethyl acetate, tetrahydrofuran or mixtures thereof, preferably toluene gives the aromatic ketone compound of formula-X,



Formula - X

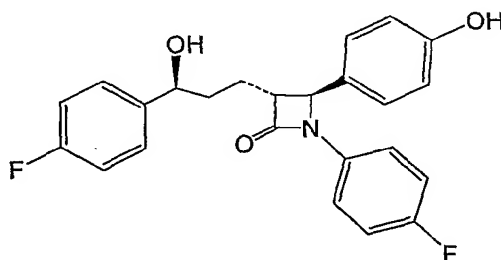
- g) Reducing the aromatic ketone compound of formula-X in presence of a chiral reducing agent such as β -chloro diisopinocampheyl borane (DIP Chloride) alone or reducing agent like borane THF and borane DMS in combination of a chiral catalyst like (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo(1,2-c)(1,3,2) oxazaborole (R-Methyl CBS) or R- Butyl CBS or R-Phenyl CBS in a

suitable solvent like methylene chloride, toluene, xylene, ethyl acetate, preferably methylene chloride followed by isolation of compound as a solid using an organic solvent to obtain hydroxy compound of formula-XI,



Formula-XI

- h) Debenzylating the compound of formula-XI with palladium carbon in a suitable solvent like such as alcoholic solvents like methanol, isopropyl alcohol, tertiary butanol, or chloro solvents like methylene chloride, chloroform, preferably isopropyl alcohol, methanol, more preferably methanol to give the compound of formula-I.



Formula-I

- The process according to claim 1 b), reaction is carried out in a suitable solvent from the group consisting of methylene chloride, chloroform, toluene, ethyl acetate and mixtures thereof, preferably methylene chloride.
- The acid trapping agent according to claim 1 b) is triethyl amine, diisopropyl ethyl amine or inorganic bases like sodium carbonate, potassium carbonate, preferably triethyl amine.
- The chiral auxiliary according to claim-1 b) is (S)-4-phenyl-2-oxazolidinone (S-POZ) or (S)-4-benzyl-2-oxazolidinone, preferably (S)-4-phenyl-2-oxazolidinone.

5. The process according to claim 1 e), solvent is selected from the group consisting of alcohols like ethanol, isopropyl alcohol, tertiary butanol or ketonic solvents like acetone, methyl isobutyl ketone and mixtures thereof, preferably acetone.
6. The base according to claim 1 e) is alkali or alkaline earth metal alkoxides or alkali or alkaline earth metal hydroxides, carbonates or bicarbonates, preferably alkali metal hydroxide, most preferably sodium hydroxide.
7. The transition metal acetate or halide according to claim-1 f) is palladium, cobalt, nickel, iron, rhodium acetate or halide, preferably transition metal acetates, more preferably palladium acetate.
8. Use of palladium acetate for the preparation of compound of formula-X from compound of formula-IX according to claim 1 f).
9. The process according to claim 1 g), the reaction is carried out in a suitable solvent at an ambient temperature, wherein the solvent is selected from the group consisting of methylene chloride, toluene, xylene or ethyl acetate and mixtures thereof, preferably methylene chloride.
10. The chiral reducing agent according to claim 1 g) is β -chloro diisopinocampheyl borane (DIP Chloride), for reducing the compound of (3R,4S)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl) azetidin-2-one.
11. The chiral catalyst according to claim 1 g) is (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo(1,2-c)(1,3,2) oxazaborole (R-Methyl CBS) or R-Butyl CBS or R-Phenyl CBS, preferably R-Methyl CBS.
12. An organic solvent for isolation of compound of formula-XI as a solid according to claim 1 g) is selected from methanol, isopropanol, toluene, hexanes, ethers, preferably ethers, more preferably diisopropyl ether.
13. Use of pivaloyl chloride for the preparation of compound of formula V from compound of formula III according to claim 1 b).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2006/000053

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁸: **C07D 205/08** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁸: C07DDocumentation searched other than minimum documentation to the extent that such documents are included in the fields searched
----Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS-databases, EPOQUE: EPODOC, WPI, EMBASE, NPL, XPESP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/049592 A1 (HETERO DRUGS LIMITED) 2 June 2005 (02.06.2005) <i>scheme A</i>	1, 5-12
	--	
A	US 5856473 (SHANKAR) 5 January 1999 (05.01.1999) <i>column 2-3</i>	1, 5-12

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
30 June 2006 (30.06.2006)Date of mailing of the international search report
10 July 2006 (10.07.2006)Name and mailing address of the ISA/ AT
Austrian Patent Office
Dresdner Straße 87, A-1200 ViennaAuthorized officer
SLABY S.

Facsimile No. +43 / 1 / 534 24 / 535

Telephone No. +43 / 1 / 534 24 / 348

Continuation of first sheet

Continuation No. II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 2, 3, 4 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Contrary to the requirements of Article 6 PCT, claims 1 (partly), 2, 3 and 4 does not clearly define the subject-matter for which protection is sought:
Claims 2-4 are not clear, since they refer to step (b) of claim 1, however there is no step (b) defined in claim 1.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN 2006/000053

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
US	A	5856473	1999-01-05	WO	A1	9716424	1997-05-09
				AU	A	7472896	1997-05-22